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2. SYNOPSIS

Name of Sponsor: Daiichi Sankyo Pharma Development	**Individual Trial Table Referring to Part of the Dossier**	**(For National Authority Use Only)**
Name of Finished Product: DU-176b	**Volume**:	
Name of Active Ingredient: DU-176b	**Page**:	

Title of Trial: A Phase 2b, Randomized, Parallel-group, Double-blind, Double-dummy, Multi-center, Multi-national, Multi-dose Study of DU-176b Compared to Dalteparin in Patients Undergoing Elective Unilateral Total Hip Replacement

Investigators and Trial Center(s): This study was conducted in Canada, Denmark, England, Latvia, Russia, Ukraine, and the United States at 61 investigative centers, 53 of which screened subjects. Information on all investigators is provided in Appendix 16.1.4.

Publication (reference): None.

Trial Period: **Initiation Date (First Subject Visit)**: 31 May 2006 **Completion Date (Final Subject Visit)**: 09 Jun 2007	**Phase of Development**: 2b

Trial Objectives: The primary objective of this study was to assess the efficacy of DU-176b in the prevention of venous thromboembolism (VTE).

The secondary objectives were to compare the incidence of VTE and major and clinically relevant non-major bleeds in subjects treated with DU-176b to subjects treated with dalteparin and to assess the pharmacokinetic (PK) and pharmacodynamic (PD) properties of DU-176b.

Additional objectives included the assessment of all bleeding events, treatment-emergent adverse events (TEAEs), laboratory test values, vital signs, and electrocardiograms (ECGs) in the DU 176b and the dalteparin treatment groups.

Methodology: This was a randomized, parallel group, multi-dose, active-controlled, double-blind, double-dummy, multi-center, multi-national study. This study was conducted in male and female subjects ≥ 18 years of age who were admitted to the hospital for elective, unilateral, total hip replacement. The investigational product DU-176b (15, 30, 60, and 90 mg doses) and matching placebo were administered orally once daily and the comparator, dalteparin (initial dose 2500 [IU]; 5000 IU for subsequent doses), and matching placebo were administered by subcutaneous injection once daily for a minimum of 7 days to a maximum of 10 days after surgery. Treatment with the study drug was planned to begin 6 to 8 hours after hip replacement surgery.

Each subject was to continue study drug for the next 7 days. (Subjects could continue the study drug for up to 10 days to ensure scheduling of the venogram within 24 hours of the last dose of study drug.) The end-of-treatment (EOT) visit was to be completed 7 to 10 days after initiation of study drug. Subjects were to complete follow-up visits at 30 ± 3 days and 60 ± 3 days after the last dose of study drug.

Name of Sponsor: Daiichi Sankyo Pharma Development	**Individual Trial Table Referring to Part of the Dossier**	**(For National Authority Use Only)**
Name of Finished Product: DU-176b	**Volume**:	
Name of Active Ingredient: DU-176b	**Page**:	

Duration of Treatment: Subjects were to receive study drug for a minimum of 7 days to a maximum of 10 days. The total length of participation for each subject was planned to be approximately 3.5 months.

Number of Subjects:

Planned: Approximately 975
Planned with Evaluable Venograms: Approximately 750
Enrolled/Randomized: 903
With Evaluable Venograms: 773
Safety Set: 896
Safety Set Completed: 808
Safety Set Discontinued: 88

Diagnosis and Main Criteria for Inclusion:

The study population comprised male and female subjects ≥ 18 years of age who were admitted to the hospital for elective unilateral total hip replacement. Subjects with hereditary or acquired bleeding or coagulation disorders, increased risk for thromboembolic events, increased risk of bleeding, or contraindications to venography were excluded. Subjects on long-term oral anticoagulants or anti-platelet agents were also excluded.

Investigational Product and Comparator Information:

Subjects in each treatment group received active drug (DU-176b or dalteparin) and placebo injections (DU-176b groups) or placebo tablets (dalteparin group). DU-176b (15 mg and 30 mg strengths) and matching placebo were supplied as yellow, film coated tablets in foil blister packs. Dalteparin (25000 IU/mL) and matching placebo were supplied in liquid form in multi-dose vials. DU-176b (15, 30, 60, and 90 mg doses) and matching placebo tablets were administered orally once daily for 7 to 10 days. The comparator drug, dalteparin (5000 IU), and matching placebo were administered by subcutaneous injection once daily for 7 to 10 days. The first dose of dalteparin was 2500 IU. The injection volume was 0.1 mL for the first dose and 0.2 mL for subsequent doses.

Lot Nos.:

DU-176b 15 mg tablets and matching placebo: [redacted], respectively
DU-176b 30 mg tablets and match placebo [redacted] respectively
Dalteparin: [redacted]
Placebo to match dalteparin: [redacted]

Criteria for Evaluation:

The primary endpoint was the incidence of VTE. The secondary endpoints were the incidence of major and clinically relevant non-major bleeding events and the PK/PD properties of DU-176b.

Name of Sponsor: Daiichi Sankyo Pharma Development	**Individual Trial Table Referring to Part of the Dossier**	**(For National Authority Use Only)**
Name of Finished Product: DU-176b	**Volume**:	
Name of Active Ingredient: DU-176b	**Page**:	

Statistical Methods:

The primary analysis was to estimate the incidence of VTE and its individual components (proximal deep vein thrombosis [DVT] and/or symptomatic pulmonary embolism [PE]) for each dose group of DU-176b and the active control, dalteparin, with 95% confidence intervals (CIs). Fisher's exact test was used to test the hypothesis of equal incidence versus dalteparin for each DU-176b dose group. Descriptive statistics were also provided. The dose-response relationship in VTE incidence among the DU-176b dose groups was assessed using the Cochran Armitage trend test. The secondary analysis was to estimate the incidence of major VTE including DVT, PE, and all cause mortality for each treatment group with 95% CIs. The other secondary variables, prothrombin time (PT) and activated partial thromboplastin time (aPTT), were summarized by treatment group at time of assessment using descriptive statistics.

For the primary safety analysis, the proportion of subjects with major and clinically relevant non major bleeds within each treatment group was estimated with 95% CIs. Fisher's exact test was used to test the hypothesis of equal incidence versus dalteparin for each DU-176b dose group. For the secondary and other safety analyses, the proportion of subjects with any bleeds including major, clinically relevant non-major, and minor bleeding events within each treatment group was estimated with 95% CIs. Treatment-emergent adverse events (TEAEs) were summarized by treatment group. Clinical laboratory tests, vital signs, and ECG parameters were summarized by treatment group.

Plasma drug concentrations were used to conduct PK analyses; a population approach was used. The results of the PK analyses are provided in Appendix 16.1.13.1. The plasma concentrations and PT and aPTT results were summarized by treatment group.

Subject Disposition and Demography Results:

A total of 903 subjects were randomized and 896 were included in the safety set (ie, all subjects who received at least one dose of study drug and had at least one post-dose safety assessment). Of the subjects included in the safety set, 724 received DU-176b and 172 received dalteparin. Of the subjects in the safety set who received DU-176b, 192 were in the 15 mg group, 170 were in the 30 mg group, 185 were in the 60 mg group, and 177 were in the 90 mg group. A total of 808 subjects completed the study: 181 (94%) in the DU-176b 15 mg group, 151 (89%) in the DU 176b 30 mg group, 164 (89%) in the DU-176b 60 mg group, 155 (88%) in the DU-176b 90 mg group, and 157 (91%) in the dalteparin group.

Most of the subjects in the safety set were Caucasian ($\geq$ 96% in each treatment group) and more than half of the subjects in each treatment group were women (range across treatment group: 52.5% to 65.3%). The mean age across treatment groups ranged from 57 to 59 years. The distribution of subjects by age group was similar across treatment groups with approximately 65% of subjects in each treatment group <65 years of age.

Efficacy Results:

The full analysis set (FAS) included all subjects who were randomized and received at least one dose of study drug and had either evaluable mandatory venogram or symptomatic VTE during the treatment period. The per protocol set (PPS) included all subjects who were in the FAS, had no major protocol deviations, and took more than 80% of planned study drug (took a total of 6 or more doses without missing doses on 2 consecutive days).

Name of Sponsor: Daiichi Sankyo Pharma Development	**Individual Trial Table Referring to Part of the Dossier**	**(For National Authority Use Only)**
Name of Finished Product: DU-176b	**Volume**:	
Name of Active Ingredient: DU-176b	**Page**:	

For PPS subjects, the overall incidence of VTE through the EOT visit for subjects treated with DU-176b was 19% (116 subjects [95%CI: 16%, 23%]). By DU-176b treatment group, the incidence of VTE progressively decreased with higher dosing strengths: 29% (47/162 subjects [95%CI: 22%, 37%]) in the 15 mg group, 20% (29/143 subjects [95%CI: 14%, 28%]) in the 30 mg group, 16% (24/153 subjects [95%CI: 10%, 22%]) in the 60 mg group, and 12% (16/139 subjects [95%CI: 7%, 18%]) in the 90 mg group. The incidence of VTE through the EOT visit in subjects treated with dalteparin was 46% (63/137 subjects [95%CI: 37%, 55%]).

The incidence of VTE in the PPS through the EOT was significantly (max $p \leq 0.003$) lower in each DU-176b treatment group than in the dalteparin comparator group. The lowest incidence of VTE was observed in groups who received higher doses of DU 176b and the dose response across DU 176b treatment groups was statistically significant ($p < 0.001$). Asymptomatic distal DVT was the most common type of adjudicated VTE across treatment groups. Secondary analyses for incidence of VTE supported the primary efficacy analysis.

As observed for the incidence of VTE, the incidence of major VTE, which included proximal DVT, symptomatic PE, and all cause mortality, was lower in all DU-176b treatment groups than in the dalteparin comparator group. A dose-related effect on the incidence of major VTE was apparent in the DU 176b treatment groups, with a lower incidence of major VTE observed in groups receiving higher dosing strengths. For PPS subjects, the overall incidence of major VTE for subjects treated with DU-176b was 4% (21/597 subjects). The proportion of subjects treated with DU 176b who had major VTE progressively decreased with higher dosing strengths: 7% (11/162 subjects) in the 15 mg group, 4% (5/143 subjects) in the 30 mg group, 2% (3/153 subjects) in the 60 mg group, and 1% (2/139 subjects) in the 90 mg group. The proportion of subjects treated with dalteparin who had any major VTE was 15% (20/137 subjects). With the exception of the occurrence of PE in a single subject in the DU-176b 60 mg group, all occurrences of major VTE were proximal DVT. No occurrence of mortality was reported for the PPS through the EOT visit. In the PPS, the difference in the incidence of major VTE between each DU-176b treatment group versus dalteparin was statistically significant ($p \leq 0.001$ to $p = 0.035$) as was the dose response across DU-176b treatment groups ($p = 0.008$).

The mean change from baseline in PT was largest in the DU-176b higher dose groups and smallest in the dalteparin group. The mean change from baseline in aPTT was largest in the DU 176b higher dose groups and smallest in the DU-176b low dose group.

Safety Results:

The primary safety variable was the incidence of major and clinically relevant non major bleeding events. The proportion of subjects in the safety set who had major or clinically relevant non major bleeding events ranged from 1.6% to 2.3% across DU-176b treatment groups. Two subjects (1.1%) in the DU-176b 90 mg group had a major bleeding event; 1 subject in each of the other DU-176b treatment groups had a major bleeding event. The proportion of subjects who had clinically relevant non-major bleeding events ranged from 1.0% to 1.7% across DU-176b treatment groups. No subject in the dalteparin group had a major or clinically relevant non-major bleeding event. The differences in the adjudicated incidence of major or clinically relevant non-major bleeding events through 10 days after the first dose of study drug were not statistically significant in comparisons of DU-176b with dalteparin. There was not a statistically significant dose response in this variable across DU 176b treatment groups

Name of Sponsor: Daiichi Sankyo Pharma Development	**Individual Trial Table Referring to Part of the Dossier**	**(For National Authority Use Only)**
Name of Finished Product: DU-176b	**Volume**:	
Name of Active Ingredient: DU-176b	**Page**:	

The proportion of subjects who had TEAEs was approximately 30% to 40% across treatment groups, with the highest incidence observed in the DU-176b 90 mg group and the lowest incidence observed in the DU-176b 30 mg group. Overall, the most common TEAEs were procedural pain, nausea, pyrexia, peripheral edema, and constipation. The incidence of pyrexia, nausea, and peripheral edema was higher in the DU-176b 15 mg group than in the other treatment groups, and the incidence of constipation was highest in the DU-176b 90 mg group. The incidence of procedural pain was comparable across treatment groups.

The proportions of DU-176b-treated subjects who had TEAEs considered related to study drug were largest in the 60 mg and 90 mg groups. Increased aspartate aminotransferase (AST) was the most common study drug related TEAE in subjects who received DU-176b (1.2%).

The 4 subjects who died were in the DU-176b lower dose groups. All the deaths were cardiac related and expected in this study population. Two subjects not in the primary efficacy population (the PPS) died within 10 days of beginning the study drug and 2 additional subjects died more than 10 days (beyond the EOT visit) after beginning study drug.

The proportion of subjects who had SAEs was largest in the DU-176b 90 mg group (5.6%) and smallest in the dalteparin group (1.7%). Most of the SAEs were related to other vascular, cardiac, and respiratory disorders or procedural complications and were within the expectations for the study population. A small number of subjects (6/728 subjects [0.8%] treated with DU 176b and 0/175 subjects [0%] treated with dalteparin) had DVT events that met the SAE definition. The incidence of DVT events meeting SAE criteria was comparable across the DU 176b treatment groups. Among the relatively few subjects who had SAEs considered by the investigator to be related to the study drug, the largest proportion was in the DU-176b 90 mg group (2.3%). The only study drug related SAE observed in more than 1 subject in any treatment group was hematoma, which was observed in 1 subject in the DU-176b 15 mg group and 1 subject in the DU-176b 60 mg group.

The proportion of subjects who discontinued the study drug due to an AE was largest in the DU 176b 90 mg group with 4%. Bleeding events led to the withdrawal of study drug from 6 subjects treated with DU-176b and no subject treated with dalteparin. Abnormal LFTs led to the withdrawal of study drug from 2 subjects in the DU-176b 90 mg group and 1 subject in the dalteparin group.

The SAEs and AEs that led to withdrawal of the study drug were relatively few and within expectations for this population. In comparison with the dalteparin group, a larger proportion of subjects in the DU-176b groups had shifts from normal at baseline to high at the EOT visit in bilirubin results. A shift in total bilirubin from normal at baseline to high at the EOT visit was observed in only 1 subject in the dalteparin group; this shift was observed in 4.2% (30 subjects) in the combined DU-176b treatment group. Shifts from normal at baseline to high at the EOT visit in other LFTs were observed in comparable proportions of subjects in the combined DU 176b group and the dalteparin group. In comparison with the dalteparin group, shifts from normal at baseline to high at the EOT visit in PT values were observed in considerably larger proportions of subjects in the DU-176b treatment groups. Comparable proportions of subjects in the DU-176b and dalteparin treatment groups had abnormal LFT results after the initial dose of study drug. No remarkable findings or dose-related trends were noted in analyses of vital signs measurements, physical examination results, or ECG data.

Name of Sponsor: Daiichi Sankyo Pharma Development	**Individual Trial Table Referring to Part of the Dossier**	**(For National Authority Use Only)**
Name of Finished Product: DU-176b	**Volume**:	
Name of Active Ingredient: DU-176b	**Page**:	

Conclusions:

The incidence of VTE was significantly lower in each DU-176b treatment group in comparison with the dalteparin comparator group. The lowest incidence of VTE was observed in groups who received higher doses of DU 176b and the dose response across DU-176b treatment groups was statistically significant. The incidence of major bleeding events in each DU-176b group was low (≤ 1.1%) and comparable among the DU-176-b groups, and, in contrast to the efficacy results, no dose response was observed. No statistically significant differences in the incidence of bleeding events were observed between the DU-176b group and dalteparin or in comparisons across DU-176b treatment groups. These findings taken together show a statistically significant, dose related response for DU-176b in preventing VTE with no statistically significant, dose related differences in the incidence of bleeding events.

Dose-related increases in PT and aPTT were associated with DU-176b treatment.

All DU-176b dose groups had point estimates for the primary efficacy outcome that were lower than dalteparin, with the DU-176b regimens showing relative risk reductions of 36% to 75% compared with dalteparin, suggesting this drug has a wide therapeutic window.

The DU-176b and dalteparin treatment groups were comparable in terms of the incidence of aminotransferase and bilirubin abnormal values.

There were 4 deaths during the study in the two DU-176b lower dose groups versus no deaths in the dalteparin group. Three of the 4 subjects who died had autopsies, with findings for the primary cause of death as acute myocardial infarction for 2 subjects and pulmonary heart disease for 1 subject. One subject, who died of cardiovascular insufficiency, did not have an autopsy, therefore fatal PE could not be confirmed or excluded as the cause of death.

Once daily dosing with DU-176b was safe and effective in the prophylaxis of DVT.

Date of the Report: 07 Nov 2007